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REMARKS

During the July 8, 2005 telephone conference with Ms. Marucci, the Examiner stated that applicants' May 19, 2004 Amendment would not be entered. Therefore, claims 1-24 and 26-43 are pending, claims 8, 10, 12, 31, 32, 35, 36 and 39 are withdrawn, and claims 44-52, which were added in the May 19, 2004 Amendment, have not been entered.

Applicants have hereinabove cancelled claims 1-26, 29-32, 34-36, 38-39, and 41-43 without prejudice or disclaimer to their right to pursue the subject matter of these claims in this or a future application. In addition, applicants have hereinabove amended claims 27, 28 and 40 and added new claims 53-57. Support for these amendments may be found inter alia in the specification as follows: claim 53: claim 27 and cancelled claims 1, 2, 5-7, 11, 15-17 and 44-50; claim 54: claim 28 and cancelled claims 1, 2, 5-7, 11, 15-16, 44 and 46-50; claim 55: claim 33 and cancelled claims 1, 2, 5-7, 11, 15-17 and 44-50; claim 56: claim 37 and cancelled claims 1, 2, 5-7, 11, 15-17 and 44-50; claim 57: claim 40 and cancelled claims 1, 2, 5-7, 11, 15-17 and 44-50. The remaining changes to the claims merely introduce minor grammatical and format changes. In making these amendments, applicants neither concede the correctness of the Examiner's rejections nor abandon their right to pursue embodiments of the instant invention no longer claimed in this application. These amendments do not involve any issue of new matter. Therefore, entry of this Amendment is respectfully requested such that claims 27, 28, 33, 37, 40, and 53-57 will be pending and under examination.

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Applicants note that the claims are hereinabove amended as discussed during the July 8, 2005 and August 4, 2005 telephone conferences between the Examiner and Ms. Marucci.

Since the Examiner did not enter applicants' May 19, 2004 Amendment, applicants again set forth below their response to the November 19, 2004 Final Office Action for completeness of the record.

Once more applicants maintain that in view of the preceding amendments and the arguments set forth below, the Examiner's grounds of rejection have been overcome. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these rejections.

Formalities

Applicants acknowledge the Examiner's withdrawal of the objection to claims 2, 5, 16, 21, and 29.

Applicants also acknowledge the Examiner's withdrawal of the rejection of claims 1-7, 9, 11, 13-19, 21, 25, and 27-30 under 35 U.S.C. §112, 2nd paragraph.

Election/Restrictions

The Examiner stated that applicants continue to traverse the withdrawal of non-elected claims 8, 10, 12, 31, and 32 in the paper filed September 17, 2004. The Examiner stated that the restriction requirement of Groups II-VIII and X, claims 8, 10, 12, 31, 32, is still deemed proper and remains final. The Examiner stated that new claims 35, 36, and 39 are also withdrawn

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from consideration as they are drawn to non-elected Group II.

In response, applicants respectfully traverse the Examiner's restriction. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove cancelled claims 8, 10, 12, 31, 32, 35, 36, and 39 without prejudice or disclaimer to their right to pursue these claims in the future.

Claim Objections

The Examiner maintained the objection to claims 17-19 for the reasons of record stated in the Office action mailed March 18, 2004. The Examiner stated that applicants' arguments have been fully considered but are not found fully persuasive.

In response, applicants respectfully traverse the Examiner's rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove cancelled claims 17-19 without prejudice or disclaimer to their right to pursue these claims in the future. Thus, this ground of rejection is now moot.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner maintained the rejection of claims 20, 22-24, 26, and 40-42 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention for the reasons of record stated in the office action mailed

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March 18, 2004.

In response, applicants respectfully traverse the Examiner's rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove cancelled claims 20, 22-24, 26, 41 and 42 without prejudice or disclaimer to their right to pursue these claims in the future. Thus, this ground of rejection is now moot.

In response to the Examiner's rejection of claim 40, applicants, without conceding the correctness of the Examiner's rejection but to expedite prosecution of the subject application, have hereinabove amended claim 40 such that it no longer recites "or" after step (b).

In view of the above remarks, applicants maintain that claim 40, as amended, satisfies the requirements of 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 20, 22-24, and 26 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the office action mailed March 18, 2004. The Examiner stated that applicants' arguments were fully considered but were not found fully persuasive.

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The Examiner also rejected claims 6, 11, 20, 22-24, 26, 30, 34, 38 and 41 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an expression silencing system comprising a nucleotide sequence encoding the T7 RNA polymerase, and pT7, allegedly does not reasonably provide enablement for functional equivalents or fragments of nucleotide sequences encoding T7 RNA polymerase, pT7, and the NOS terminator; the expression silencing system wherein the target sequence is a non-coding sequence in the plant genome. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record stated in the office action mailed March 18, 2004. The Examiner stated that applicants' arguments were fully considered but were not found fully persuasive.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove cancelled claims 6, 11, 20, 22-24, 26, 30, 34, 38 and 41 without prejudice or disclaimer to their right to pursue these claims in the future. Thus, this ground of rejection is now moot.

Claim Rejections Under 35 U.S.C. §102(b)

The Examiner maintained the rejection of claims 1-7, 13-15, 17 and 43 under 35 U.S.C. §102(b) as being anticipated by Lassner et al., for the reasons of record stated in the office action mailed March 18, 2004. The Examiner stated that applicants' arguments

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are fully considered but are not found fully persuasive.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove cancelled claims 1-7, 13-15, 17 and 43 without prejudice or disclaimer to their right to pursue these claims in the future. Thus, this ground of rejection is now moot.

Claim Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-7, 9, 13-17, 20-24, 26, 27-30, 33, 34, 37, 38, and 40-43 under 35 U.S.C. §103(a) as allegedly being unpatentable over Lassner et al. in combination with Blockland et al., (*Plant J.*, 1994, Vol. 6, pages 861-877), and Palauqui et al. (*EMBO J.*, 1997, vol. 16, pages 4738-4745), for the reasons of record stated in the office action mailed March 18, 2004. The Examiner stated that applicants' arguments are fully considered but are not found fully persuasive.

The Examiner stated that applicants argued that a *prima facie* case of obviousness was not made out, and submitted a declaration under 37 C.F.R. §1.132, signed by co-inventor Dr. Ilan Sela, in support. The Examiner stated that the declaration states that the T7 silencing system differs from other silencing systems in that no siRNA could be detected, the silencing signal was not transduced across grafts, and the viral silencing suppressor He-Pro could not overcome the silencing effect. The Examiner stated that the declaration states that the T7 silencing system activity was confined to the nucleus, as silenced genes were methylated and pertinent siRNAs were detected in nuclear extracts, and dicer

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activity was enhanced (response, pages 50-51; declaration, item 21). The Examiner stated that however, these differences are not described in the specification as filed, nor are they encompassed by the claims. The Examiner stated that further, the information in the declaration regarding the inability of the silencing signal to transduce across grafts (also discussed in items 27-30) directly contradicts the instant specification. The Examiner stated that Example 4 of the specification teaches that in 3 of 6 plants tested, the silencing signal did transduce across grafts. The Examiner stated that page 4 of the specification states that "the invention relates to a method for producing a transgenic plant carrying a substantially silenced target sequence by grafting a plant, or parts thereof, carrying and expressing said silent target sequence on a transgenic plant obtained by the process of the invention." The Examiner stated that further, it is noted original claim 25 required grafting, and this claim was only cancelled in applicants' most recent response.

The Examiner stated that the declaration also points out supposed deficiencies of Blockland et al. (items 22-25). The Examiner stated that however, applicants are arguing against the reference alone, not in combination with the other reference. The Examiner stated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. The Examiner stated that the declaration also states that another unique characteristic of the T7 silencing system is the capacity of using only a short homology fragment, around 70 nucleotides (item 26). The Examiner stated that however, the claims are not limited to using only such fragments.

In response, applicants respectfully traverse the Examiner's

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rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove cancelled claims 1-7, 9, 13-17, 20-24, 26, 29-30, 34, 38, and 41-43 without prejudice or disclaimer to their right to pursue these claims in the future. Thus, this ground of rejection is now moot.

In response to the Examiner's rejection of claims 27, 28, 33, 37 and 40, applicants note that the now claimed invention is directed to methods of silencing the expression of a target gene in a plant. In this regard, applicants respectfully traverse the Examiner's rejection, and again maintain that the Examiner has failed to establish a prima facie case of obviousness against the rejected claims.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that such a combination would have succeeded.

Applicants contend that the references cited against the rejected claims fail to support a prima facie case of obviousness.

To support a case of prima facie obviousness, Lassner et al., Blokland et al., and Palauqui et al., when combined, would have to teach or suggest all elements of the rejected claims. Moreover, there would have to have been a motive to combine them, and a reasonable expectation of the invention's success at the

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time of the invention. The references fail to do so.

As previously explained, Lassner et al. teach the possibility of combining the use of the prokaryote T7 RNA polymerase gene with regulatory elements which are functional in plants, for successful gene expression: "This system demonstrates the feasibility of T7 RNA polymerase-based approaches for the high-level expression of introduced gene's in plant cells" (Lassner et al., abstract, page 229, last sentence). Therefore, it is clear that the objective of these authors was to achieve a functional T7 RNA polymerase driven expression system in plants.

For a person of skill in the art, the conclusion that could be reached from Lassner et al. is that a nucleotide sequence regulated by the T7 promoter should be overexpressed when transfected into plant cells already expressing the T7 RNA polymerase.

The T7 expression system should not necessarily interfere with the expression of endogenous genes driven by their own endogenous promoters. No allusion regarding this possibility was mentioned or insinuated in the Lassner et al. paper. Lassner et al. conclude by saying: "These experiments are a step in the development of a T7 RNA polymerase-mediated gene expression system for plants" (see discussion in page 233, first line in last paragraph). Based on this, it appears that the authors did not see any potential of using the T7 RNA polymerase for silencing purposes, but only using T7 RNA polymerase for expression purposes.

It may be mentioned at this point, that notwithstanding the many years that passed since the publication of Lassner et al., even

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today available commercial kits employing T7 RNA polymerase are intended for high level and efficient expression. For example, the Technical Bulletin 8033-1 (from Invitrogen Life Technologies) describes the T7 RNA polymerase uses as follows: "T7 RNA polymerase initiates synthesis at the T7 promoter sequence and produces an RNA transcript of the DNA. The RNA transcripts are used as hybridization probes for DNA and RNA blots and in situ studies, in ribonuclease protection assays where the transcript is hybridized with target mRNA sequences, to study post-transcriptional modifications including RNA splicing and polyadenylation, and for in vitro translation".

Other available T7 RNA polymerase kits from Stratagen (USA) are also intended to be used for producing: "probes for nucleic acid hybridizations, templates for in vitro translations, substrates for RNA processing studies and exon and intron mapping of genomic DNA."

Furthermore, publications such as:

- 1) Alexander, W.A., Moss, B., Fuerest, T.R. (1992) Regulated expression of foreign genes in Vaccinia virus under the control of bacteriophage T7 RNA polymerase and the E. coli lac repressor. *J. Virol.* 66:2934-2942 (Exhibit A); and
- 2) Fuerest, T.R., Nile's, E.G., Studier, F.W., Moss, B. (1986). Eukaryotic transient expression system based on recombinant vaccinia virus that synthesizes Bacteriophage T7 RNA polymerase. *Proc. Natl. Acad. Sci. USA* 83:8122-8126 (Exhibit B),

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are further examples reflecting the use of T7 RNA polymerase in mammals at the time of the invention. These articles teach one of skill in the art that the T7 RNA polymerase/T7 RNA promoter system is an efficient eukaryotic expression system.

Turning to Blockland, the Examiner has formerly argued that it would have been obvious and within the capabilities of one of ordinary skill in the art at the time the invention was made to use the RNA polymerase/pT7 system of Lassner et al. to silence a gene of interest in plant cells, for example the *chs* gene of Blockland et al.

Applicants respectfully traverse. Throughout Blockland et al., it is stated or implied that the level of transcription is not a prerequisite for inducing silencing. For example: "Surprisingly, even a promoterless *chs* transgene construct was found to suppress the endogenous *chs* genes in three out of 15 transformants" (Summary, lines 23-26). And also: "It remains, however, unknown whether or not transcription of the transgene locus is required to induce co-suppression" (Summary, lines 26-28). Furthermore: "As mentioned before, the variation in transgene transcription levels in the various transformants was quite dramatic, but neither a high nor a low level correlated with co-suppression" (Results, page 866 right column, second paragraph, line 9) and: "The results described in the previous section indicate that suppression of endogenous genes does not require highly expressed transgenes" (Results page 866, Chs suppression by a promoterless chsA transgene paragraph, first line).

Therefore, although Blockland et al. might teach crossing plants carrying different constructs in order to achieve silencing, it would not have been reasonable to introduce a "foreign potent

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expression system", as the T7 RNA polymerase/T7 promoter to trigger silencing, if gene silencing may be effected even with a promoterless construct.

There is nothing in Blockland et al. which would have motivated one skilled in the art to employ the expression system of Lassner et al. One of skill in the art would not use an efficient RNA polymerase, whose normal function is to transcribe mRNA from DNA sequences, with the final aim of gene expression, for the purpose of silencing such gene expression.

At the time of the invention, this concept seemed contradictory and it was definitively not obvious. The scientific rationale supporting this expression-silencing idea is in fact revolutionary.

With regards to Palauqui et al., this reference teaches co-suppression of plant host genes and transgenes that can be transmitted efficiently from silenced stocks to non-silenced scions expressing the corresponding transgene.

Given this information, it is clear that the T7-driven silencing system of the subject invention is not based on Lassner et al. in combination with Blokland et al. and/or Palauqui et al., but is a new system mediated by a different mechanism.

Accordingly, the Examiner has failed to establish the prima facie obviousness of claims 27, 28, 33, 37, and 40 as amended over these references.

Finally, on page 8 of the pending Office Action, lines 17 to 19, the Examiner states: "Further, the information in the declaration

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regarding the inability of the silencing signal to transduce across grafts (also discussed in item 27-30) directly contradicts the instant specification".

Applicants respectfully disagree with the characterization of the relationship between the declaration and the specification. In science, one uses samples to draw inferences about populations but a sample does not necessarily represent the population from which it is taken. By way of explanation, errors in scientific studies generally fall into one of two major categories: (a) random errors and (b) systematic errors.

A random error occurs when one takes a sample of a variable population, and by chance the sample does not perfectly represent the real population. This is always present to some degree, because populations are naturally variable. Generally, random errors are unpredictable (make estimates either too large or too small) and have larger effects if the sample size is small, so in order to decrease the impact of random error, it is recommended to increase the sample size.

A systematic error occurs when something about the way one samples results in estimates that are consistently incorrect in some direction (either consistently too large or consistently too small). The systematic error might create bias (directional tendency towards some incorrect conclusion) and since it is caused by the sampling method, increasing sample size does not help get rid of it.

Usually, if the sample size is at least 30, one is very likely to have adequate statistical power to detect any trends that are present. Most of the times, a sample of 20 will give adequate

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statistical power. Statistical power is increased by decreasing the random error and we do that by increasing the sample size.

In the T7-driven silencing system of the invention, the silencing effect is restricted to the cells carrying the constructs themselves [as previously detailed in the inventor's Declaration Exhibit 4 (Meir et al. manuscript, Table 1)] and there is no transmission of the signal to other tissues as seen in other plants (as shown in Palauqui et al.) or other species (e.g. C. elegans). Therefore, the results presented in Example 4 (sample size = 6), are likely due to a statistical random error originated by the small number of the analyzed plants in the experiment (small size sampling group).

Any apparent discordance between the conclusions reached in the Example 4 of the specification which support the idea that "silencing is transmitted from silenced stocks to non-silenced scions expressing the corresponding transgene", and the later understanding (see declaration Exhibit 4) which lead to the opposite conclusion, can be explained by a statistical error, caused by mis-chosen group size in the first experiment.

In view of the above remarks, applicants maintain that claims 27, 28, 33, 37, and 40, as amended, satisfy the requirements of 35 U.S.C. §103(a). Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

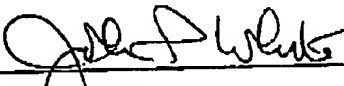
For the reasons set forth hereinabove, applicants maintain that pending claims 27, 28, 33, 37, 40, and 53-57 are in condition for allowance. Accordingly, allowance is respectfully requested.

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the \$55.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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